

Mitotically active juvenile xanthogranuloma: Alarming features of a self-resolving disease



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Key words: juvenile xanthogranuloma; mitotic figures; non-Langerhans cell histiocytosis.

INTRODUCTION

Juvenile xanthogranuloma (JXG) is the most common histiocytic disorder of childhood, classically presenting as an asymptomatic, solitary, and yellowish papulonodule on the head or neck that spontaneously regresses after 3 to 6 years.¹ The literature shows that some JXG patients develop multiple lesions; in addition, several clinical variants have been described, including micronodular, macronodular, and oral JXG.¹ The most common extracutaneous JXG is the ocular form, which may be complicated by hyphema, glaucoma, and/or blindness.^{1,2} Infrequently, the literature has described a triple association between JXG, neurofibromatosis type 1 (NF1), and juvenile myelomonocytic leukemia; in combination, these conditions confer significant mortality.³ In addition, B cell lymphoma and chronic lymphocytic leukemia have also been associated with JXG in patients with multiple lesions. Histologically, JXG typically presents with a dense dermal infiltration by histiocytes, which latter may be accompanied by inflammatory cells and multinucleated giant cells. Classically, mitotic figures are few or entirely absent.⁴ Early JXG lesions are characterized by monomorphous histiocytes with abundant eosinophilic cytoplasm while mature lesions have a lipid-rich cytoplasm, giving them a foamy appearance. Touton giant cells can be seen in up to 85% of cases.⁵

We report an unusual case of a 5-month-old Hispanic female patient presenting with multiple yellowish papulonodular lesions. Histologically, the lesions were remarkable for atypical histiocytic

Abbreviations used:

JXG: juvenile xanthogranuloma
NF1: neurofibromatosis type 1

infiltrate with Touton giant cells, elevated Ki-67, and markedly increased mitotic activity. These findings are worrisome because they might suggest the presence of a histiocytic neoplasm with possible systemic involvement.

CASE REPORT

An otherwise healthy Hispanic five-month-old girl born to a G1P1A0 mother at 38 weeks by cesarean section presented with a 2-month history of slowly growing, asymptomatic, and yellowish skin papules on her face and torso. The child's immunizations were up to date, and she had no allergies. Her mother initially noticed an elevated, reddish skin lesion on the infant's left shoulder, which measured 0.4 cm, approximately. Two months later, the lesion had increased in size, becoming yellowish and ulcerated. Simultaneously, additional similar lesions developed on the patient's face and torso. There were no associated symptoms, fever or any systemic findings.

A physical examination was remarkable for 12 discrete non-tender erythematous-to-yellow papules and nodules distributed on the infant's face, shoulders, upper back, and flanks (Fig 1). Some lesions had overlying telangiectasias while others had a

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Funding sources: None.

IRB approval status: Not applicable.

Consent statement: Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal stating that the legal guarding of the patient gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

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JAAD Case Reports 2022;29:142-5.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2022.09.007>



Fig 1. Erythematous-to-yellow papules and nodules distributed on the patient's face, shoulders, upper back, and flanks.

xanthomatous appearance with a central crust (Fig 1). The sizes of the lesions ranged from 0.5 to 1.7 cm, with the largest occurring on the left shoulder. The oral and genital mucosae were normal, and there was no lymphadenopathy or hepatosplenomegaly. The differential diagnosis at this point included benign cephalic histiocytosis, JXG, molluscum contagiosum, leukemia cutis, and cutaneous metastases.

A biopsy of 2 of the lesions on the patient's back and left flank showed a proliferation of spindle-shaped cells with a storiform pattern and a dense dermal proliferation of epithelioid histiocytes with foamy cytoplasm (Fig 2). A few Touton giant cells were found in one of the lesions. Immunohistochemistry was diffusely positive for CD4, CD68, and fascin (Fig 3). Negative markers included c-KIT, myeloperoxidase, CD1a, langerin, S100, melan-A, factor XIIIa, CD3, CD10, CD34, CD21, CD23, CD30 and pankeratin. Acid-fast and periodic aci-schiff stains were negative for organisms. Importantly, there was an increase in mitotic activity on phosphohistone H3 staining (40 per 10 hpf) and a high proliferative index on Ki-67 (60%) (Fig 3). Given these clinicopathological findings, a full workup was ordered to rule out a possible a hematologic or lymphoproliferative disorder. The child's blood counts and chemistry were normal, and computerized tomography scans of the head, chest, abdomen, and pelvis were unremarkable. No atypical flow cytometric findings or evidence of clonal lymphoid expansion, or an increase in blasts was

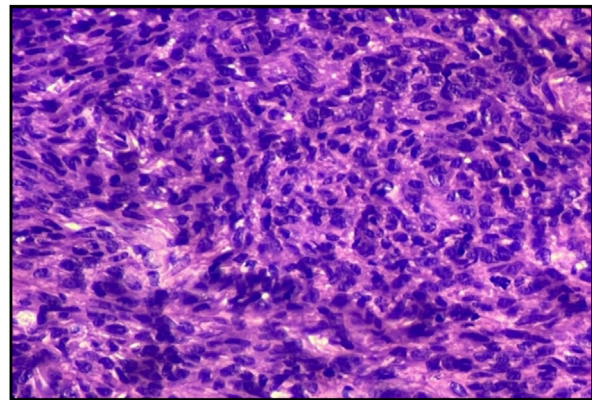


Fig 2. Hematoxylin and eosin staining. Histologic section shows a dense nodular infiltrate of epithelial cells, some with foamy cytoplasm. There is a spindle shaped proliferation with storiform arrangement.

observed on bone marrow biopsy. The ophthalmologic evaluation was unremarkable. The diagnosis of mitotically active JXG without extracutaneous involvement was made, and the patient was followed closely. Five months later, 3 of the truncal lesions had regressed spontaneously without treatment, leaving mild atrophy and hyperpigmentation; the patient continued in good health.

DISCUSSION

A clinical diagnosis is usually sufficient for classic cases of JXG; however, a histopathological diagnosis was made for this patient, given the eruptive nature and rapid evolution of her lesions. There are ancillary clinical features and tools that may help in the diagnosis of JXG. A yellow-orange background surrounded by an erythematous border with delicate branched vessels, also known as the "setting sun," may be a characteristic dermoscopic pattern of JXG.⁶ Recently, Reilly et al⁷ described diagnosing JXG on the cheek of a patient using noninvasive reflectance confocal microscopy. However, these dermoscopic features should not be considered exclusive to JXG, and differentiation from malignancies, including sarcomas, should be made with a histological workup.⁸

It is still unknown whether JXG is a neoplastic or reactive; when there are multiple lesions, the ability to make this diagnostic classification is reduced.³ Juvenile myelomonocytic leukemia is up to 30 times higher in NF1 patients with multiple JXGs than in those without JXG lesions.³ Although, there were no clinical signs of NF1 in our patient, the high proliferative index of the multifocal lesions and their sarcomatous histologic features prompted us to

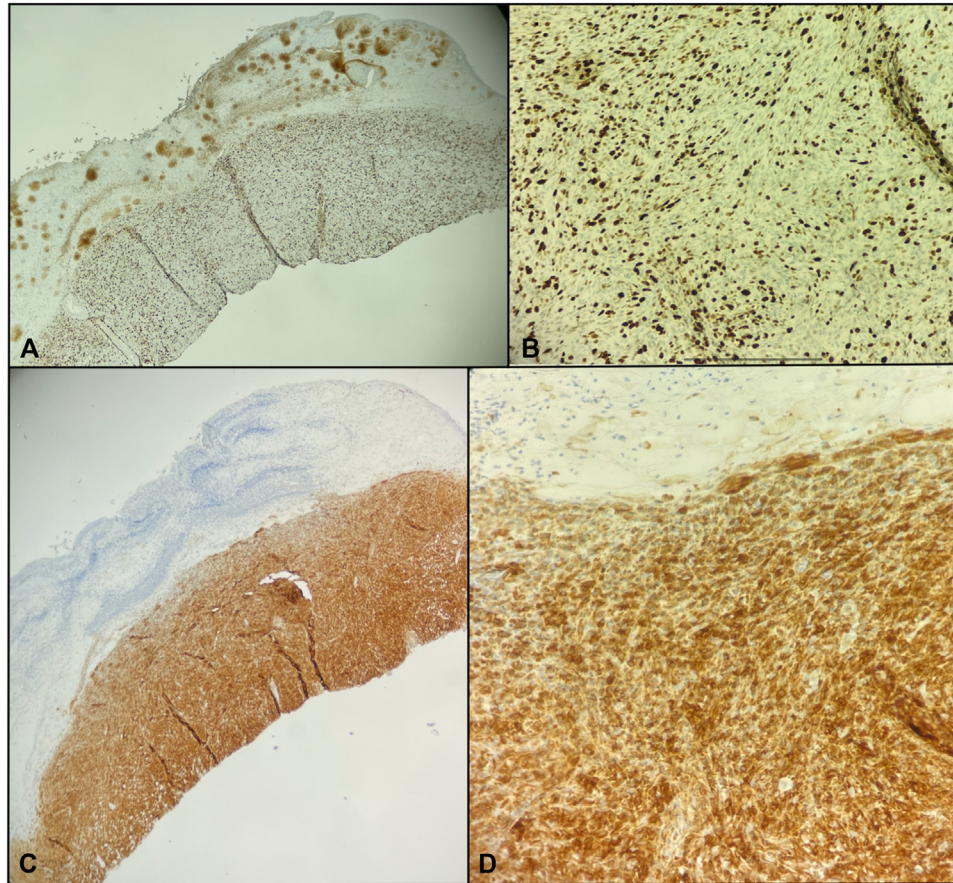


Fig 3. A and B, Ki-67 is elevated. C and D, CD68 immunostaining.

perform an invasive workup to rule out an underlying internal malignancy.

In view of the uncertainty, the high number of mitotic figures—especially in the presence of multifocal lesions—was interpreted as a possible alarming sign of an associated leukemia. Numerous mitoses were previously described in a case of deep-seated JXG presenting as a congenital cervical neck mass, though showing a lower number of mitoses (6 per 10 hpf) than were seen in this case. However, deep-seated JXG differs histologically from dermal JXG as the associated lesions are usually less circumscribed and have a lower number of Touton cells and variable necrosis.^{9,10} Similarly, a high number of mitoses (15–20 per hpf) were reported on an intramuscular JXG in a young woman, the absence of true nuclear atypia and presence of multinucleated cells argued against a diagnosis of histiocytic sarcoma.¹⁰ It is still to be determined whether a high level of mitotic figures on PHH3 staining or a high proliferative index on Ki67 is a relevant feature of some JXG lesions. A meticulous assessment of a possible malignancy should be made, with said assessment tailored to the patient. Despite the

alarming histological features, a benign clinical course was observed.

Conflicts of interest

None disclosed.

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